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Therapeutic Class Review
Lipotropics - Fibric Acid Derivatives

I. Overview

The therapeutic class called the fibric acid derivatives encompasses two chemical entities, fenofibrate and gemfibrozil. Fibric acid derivatives are agonists of the peroxisome proliferator-activated receptor (PPAR) and work by increasing lipoprotein lipase activity and triglyceride (TG) clearance. These agents also increase hepatic oxidation of fatty acids, which decreases the secretion of TG-rich lipoproteins and enhances the breakdown of very low-density lipoprotein (VLDL). Finally, fibric acid derivatives may increase secretion of cholesterol into bile.[1,2] Fibric acid derivatives generally decrease TG levels by 25%-50% and increase high-density lipoprotein cholesterol (HDL-C) concentrations by 5%-15%. They promote a shift from small, dense low-density lipoprotein (LDL) to larger, more buoyant particles, which are less susceptible to oxidation and possess higher binding affinity for removal by the nonatherogenic LDL receptor pathway.[1-3]

The fibric acid derivatives are established as effective agents for managing dyslipidemia, particularly in patients with elevated concentrations of TG-rich lipoproteins (VLDL and VLDL remnants) and low levels of HDL-C, typically associated with the dyslipidemia characteristic of type 2 diabetes and the metabolic syndrome. While hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) are regarded as the cornerstone of lipid-modifying therapy, based on their proven efficacy in reducing plasma levels of LDL cholesterol (LDL-C), they exert only modest effects on TG (decrease 15%-35%) and HDL-C (typically increase <10%).[1-3]

Gemfibrozil was approved by the Food and Drug Administration (FDA) in 1981 and has been available generically since 1993.[4] Fenofibrate is available in several formulations with generics currently available for the 54 mg and 160 mg micronized tablets, and for the 67 mg, 134 mg, and 200 mg micronized capsules. A nonmicronized formulation of fenofibrate is no longer available in the United States (US).[2] The most recently developed version of fenofibrate is the nanocrystallized formulation, which was approved in 2004.[4]

The fibric acid derivatives that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. This review does not include information on Fenoglide® (fenofibrate) which was reviewed at the October 2008 DUR meeting.

Table 1. Fibric Acid Derivatives Included in this Review

Generic Name	Formulation(s)	Example Brand Name(s)
fenofibrate, micronized	capsule, tablet	Antara®, Lipofen®, Lofibra®*, Triglide®
fenofibrate, nanocrystallized	tablet	Tricor®
gemfibrozil	tablet	Lopid®*

*Generic is available in at least one dosage form or strength.

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the fibric acid derivatives (fibrates) are summarized in Table 2.

Table 2. Treatment Guidelines Using the Fibric Acid Derivatives

Clinical Guideline	Recommendation
National Heart, Lung, and Blood Institute (NHLBI)/American College	• Therapeutic lifestyle changes (TLC) remain an essential modality in clinical management. • Fibrates may have an adjunctive role in the treatment of patients with high

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Clinical Guideline	Recommendation
of Cardiology (ACC)/American Heart Association (AHA): **Implications of Recent Clinical Trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines (2004)**[3]	triglycerides (TG) and low high-density lipoprotein cholesterol (HDL-C), especially in combination with statins. • In high-risk patients with high TG or low high-density lipoprotein (HDL) levels as the predominant lipoprotein abnormality, consideration can be given to combination therapy with fibrates or nicotinic acid and a low-density lipoprotein cholesterol (LDL-C)-lowering agent. • When an LDL-C-lowering drug therapy is employed in high-risk or moderately high-risk persons, it is advised that intensity of therapy be sufficient to achieve at least a 30%-40% reduction in LDL-C levels. If drug therapy is a component of cholesterol management for a given patient, it is prudent to employ doses that will achieve at least a moderate-risk reduction. • Standard statin doses are defined as those that lower LDL-C levels by 30%-40%. The same effect may be achieved by combining lower doses of statins with other drugs or products (eg, bile acid sequestrants, ezetimibe, nicotinic acid, or plant stanols/sterols). • When LDL-C level is well above 130 mg/dL (eg, ≥160 mg/dL), the dose of statin may have to be increased or a second agent (eg, a bile acid sequestrant, ezetimibe, or nicotinic acid) may be required. Alternatively, maximizing dietary therapy (including use of plant stanols/sterols) combined with standard statin doses may be sufficient to attain goals. • If a high-risk person has high TG or low HDL-C levels, consideration can be given to combining a fibrate or nicotinic acid with an LDL-lowering drug. When TG are >200 mg/dL, non–HDL-C is a secondary target of therapy, with a goal 30 mg/dL higher than the identified LDL-C goal. For the treatment of familial defective apolipoprotein B-100 (FDB) • TLC indicated. • All LDL-C-lowering drugs are effective. • Combined drug therapy required less often than in heterozygous FH. For the treatment of polygenic hypercholesterolemia • TLC indicated for all persons. • All LDL-C-lowering drugs are effective. • If necessary to reach LDL-C goals, consider combined drug therapy.
National Institutes of Health (NIH), National Cholesterol Education Program (NCEP): **Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III [ATP III]) Final Report (2002)**[5]	<u>General Recommendations</u> • With regards to TLC, higher dietary intakes of omega-3 fatty acids in the form of fatty fish or vegetable oils are an option for reducing risk for coronary heart disease (CHD). This recommendation is optional because the strength of evidence is only moderate at present. NCEP ATP III supports the AHA's recommendation that fish be included as part of a CHD risk-reduction diet. Fish in general is low in saturated fat and may contain some cardioprotective omega-3 fatty acids. However, a dietary recommendation for a specific amount of omega-3 fatty acids is not made. • Initiate low-density lipoprotein (LDL)-lowering drug therapy with a statin, bile acid sequestrant or nicotinic acid. • Statins should be considered as first-line drugs when LDL-lowering drugs are indicated to achieve LDL-C treatment goals. • After 6 weeks if LDL-C goal is not achieved, intensify LDL-lowering therapy. Consider a higher dose of a statin or add a bile acid sequestrant or nicotinic acid. <u>Fibric Acid Derivatives (Fibrates)</u> • Fibrates can be recommended for persons with very high TG to reduce risk for acute pancreatitis. • They also can be recommended for persons with dysbetalipoproteinemia (elevated beta-very low density lipoproteins).

Clinical Guideline	Recommendation
	• Fibrate therapy should be considered an option for treatment of persons with established CHD who have low levels of LDL-C and atherogenic dyslipidemia. • They also should be considered in combination with statin therapy in persons who have elevated LDL-C and atherogenic dyslipidemia.
American Heart Association (AHA)/American College of Cardiology (ACC) National Heart, Lung, and Blood Institute (NHLBI): **AHA/ACC Guidelines for Secondary Prevention for Patients With Coronary and Other Atherosclerotic Vascular Disease: 2006 Update (2006)**[6]	• For patients without atherosclerotic disease, including those with other risk factors, recommendations of the NCEP ATP III guidelines and their 2004 update should still be considered current. • Therapeutic options to reduce non–HDL-C include the following: more intense LDL-C lowering therapy, or niacin (after LDL-C lowering therapy) or fibrate therapy (after LDL-C lowering therapy). • If triglycerides are ≥500 mg/dL, therapeutic options to prevent pancreatitis are fibrate or niacin before LDL-lowering therapy. Treat LDL-C to goal after triglyceride-lowering therapy.
Institute for Clinical Systems Improvement (ICSI): **Healthcare Guideline: Lipid Management in Adults (2007)**[7]	• For monotherapy, statins are the drugs of choice for lowering LDL. • If a patient is intolerant to a statin, other statins should be tried before ruling them all out. • If patients are unable to take statins, then bile acid sequestrants, ezetimibe, fibric acids and niacin can be used. • Although combination therapy is not supported by outcome-based studies, some high-risk patients will require it. • Using low doses of two complementary agents can often reduce LDL to a greater extent than a higher dose of either agent, such as when a statin is combined with either ezetimibe or a bile acid sequestrant, with fewer side effects. • In very resistant cases, triple therapy may be needed.
American Heart Association (AHA): **Drug Therapy of High-Risk Lipid Abnormalities in Children and Adolescents: a Scientific Statement From the American Heart Association (2007)**[8]	• For children meeting criteria for lipid-lowering drug therapy, a statin is recommended as first-line treatment. The choice of statin is dependent upon preference but should be initiated at the lowest dose once daily, usually at bedtime. • For patients with high-risk lipid abnormalities, the presence of additional risk factors or high-risk conditions may reduce the recommended LDL level for initiation of drug therapy and the desired target LDL levels. Therapy may also be considered for initiation in patients <10 years of age. • Additional research regarding drug therapy of high-risk lipid abnormalities in children is needed to evaluate the long-term efficacy and safety and impact on the atherosclerotic disease process.
European Guidelines on Cardiovascular Disease Prevention in Clinical Practice: **Fourth Joint Task Force of the European Society of Cardiology (ESC) and Other Societies (2007)**[9]	• Statins are considered first-line drugs for lowering LDL cholesterol. • Fibric acid derivatives are considered useful only for the treatment of patients with low HDL, high TG, and other characteristics of insulin resistance syndrome and type 2 diabetes. • Fibrate monotherapy cannot be recommended as first-line therapy in diabetic patients but may be considered in those with persistently low HDL levels or severely elevated TG. • When TG are between ~450-900 mg/dL, fibrates (or statins) may be considered as first-choice drugs. • Combination therapy may be used in patients needing additional therapy to reach goals and the selection of appropriate drugs should vary based upon lipid levels.

III. Indications

Food and Drug Administration (FDA)-approved indications for the fibric acid derivatives are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Fibric Acid Derivatives[10-15]

Indication	Fenofibrate	Gemfibrozil
As adjunctive therapy to diet to reduce elevated low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), triglycerides (TG), and apolipoprotein B (apo B), and to increase high-density lipoprotein cholesterol (HDL-C) in adult patients with primary hypercholesterolemia or mixed dyslipidemia (Fredrickson Types IIa and IIb)	✔	
As adjunctive therapy to diet for treatment of adult patients with hypertriglyceridemia (Fredrickson Types IV and V hyperlipidemia)	✔	
Treatment of adult patients with very high elevations of serum TG levels (Types IV and V hyperlipidemia) who present a risk of pancreatitis and who do not respond adequately to diet		✔ *
Reducing the risk of developing coronary heart disease (CHD) only in Type IIb patients without a history of or symptoms of existing CHD, and who have the following triad of lipid abnormalities: low HDL-C levels in addition to elevated LDL-C and elevated TG		✔ †

*Patients who present such risk typically have serum TG over 2,000 mg/dL and have elevations of very low-density lipoprotein cholesterol (VLDL)-cholesterol as well as fasting chylomicrons (Type V hyperlipidemia). Subjects who consistently have total serum or plasma TG below 1,000 mg/dL are unlikely to present a risk of pancreatitis.
†Indicated only for patients who have had an inadequate response to weight loss, dietary therapy, exercise, and other pharmacologic agents (such as bile acid sequestrants and nicotinic acid) known to reduce LDL-C and raise HDL-C.

IV. Pharmacokinetics

The pharmacokinetic parameters for the fibric acid derivatives are summarized in Table 4.

Table 4. Pharmacokinetic Parameters of the Fibric Acid Derivatives[1,10-15]

Drug	Bio-availability (%)	Protein Binding (%)	Metabolism	Metabolites	Elimination (%)	Half-Life (hours)
Fenofibrate	60-90	99	Glucuronidation (liver and kidneys)	Yes; fenofibric acid, fenofibric acid glucuronide, benzhydrol metabolite	Renal (60-93)	16-23
Gemfibrozil	Not reported	99	Hepatic	Yes; carboxyl metabolite, hydroxymethyl metabolite	Renal (70)	1.5

Pharmacokinetic studies have shown that Antara® 130 mg capsule, Lipofen® 150 mg tablet, Lofibra® 160 mg tablet and 200 mg capsule and generic equivalents, Triglide® 160 mg tablet and Tricor® 145 mg nanocrystal tablet produce comparable serum fenofibrate levels. The same has been demonstrated for Lofibra® 54 mg tablet and Lofibra® 67 mg capsule and their generic equivalents. To maximize bioavailability, Lofibra® should be administered with meals, while Antara®, Tricor® and Triglide® may be administered without regard to meals.[2]

Table 5. Fenofibrate Formulations Providing Equivalent Plasma Concentrations of Fenofibric Acid[10-15]

	Antara® Micronized Capsules	Lipofen® Micronized Tablets	Lofibra® Micronized Tablets and Equivalents	Lofibra® Micronized Capsules and Equivalents	Triglide® Micronized Tablets	Tricor® Nanocrystallized Tablets
Comparable strengths			54 mg tablet*	67 mg capsule*		
Comparable strengths	130 mg capsule	150 mg tablet	160 mg tablet*	200 mg capsule*	160 mg tablet‡	145 mg tablet, or three 48 mg tablets

No information was provided in product information for Antara® 43 mg capsules, Lipofen® 50 mg capsules, Lofibra® 134 mg capsules, and Triglide® 50 mg tablets.
*Generic is available.

‡Triglide® 160 mg tablet exhibits a similar extent of absorption but 32% higher rate of absorption compared to the 200 mg micronized fenofibrate capsule under low-fat fed conditions.

V. Drug Interactions

Significant drug interactions with the fibric acid derivatives are listed in Table 6.

Table 6. Significant Drug-Drug Interactions with the Fibric Acid Derivatives[16]

Drug(s)	Significance Level	Interaction	Mechanism
Fibric acid derivatives (both)	1	Warfarin	Coagulation factor synthesis may be affected. Fibric acid derivatives may increase the hypoprothrombinemic effects of oral anticoagulants. Bleeding and death have occurred. Warfarin plasma levels are not affected.
Fenofibrate	1	Atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin	The mechanism is unknown. Severe myopathy or rhabdomyolysis may occur. If coadministration of these agents cannot be avoided, use with caution and closely monitor creatine kinase (CK). Fenofibrate has been observed to increase pravastatin area under the curve (AUC) by 28%. The AUC and maximum concentration (C_{max}) of the N-desmethyl rosuvastatin metabolite decreased by 48% and 39%, respectively. Fenofibrate does not appear to affect the pharmacokinetics of rosuvastatin.
Gemfibrozil	1	Atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin	The mechanism is unknown. Severe myopathy or rhabdomyolysis may occur. If coadministration of these agents cannot be avoided, use with caution and closely monitor CK. Gemfibrozil has been observed to increase the AUC of pravastatin, atorvastatin, simvastatin, lovastatin, and rosuvastatin. In addition, increased C_{max} has been reported with coadministration of gemfibrozil and pravastatin or rosuvastatin.
Gemfibrozil	2	Repaglinide	Inhibition of repaglinide metabolism (CYP2C8) by gemfibrozil is suspected. Repaglinide plasma concentrations may be greatly increased and prolonged, increasing the risk of severe and protracted hypoglycemia. Avoid coadministration of repaglinide and gemfibrozil. If coadministration is necessary, reduce the dose of repaglinide and closely monitor blood glucose concentrations. Adjust therapy as needed.
Gemfibrozil	2	Thiazolidine-diones (pioglitazone, rosiglitazone)	Inhibition of thiazolidinedione metabolism (CYP2C8) by gemfibrozil is suspected. Plasma concentrations of thiazolidinedione antidiabetic agents may be elevated, increasing hypoglycemic and other adverse effects (eg, peripheral and pulmonary edema) of these agents. If coadministration of a thiazolidinedione and gemfibrozil cannot be avoided, consider initiating therapy at a reduced thiazolidinedione dose, possibly as much as 50% to 70%. Closely monitor blood glucose, glycosolated hemoglobin, and thiazolidinedione adverse effects when starting or stopping gemfibrozil therapy.

Significance Level 1=major severity
Significance Level 2=moderate severity

VI. Adverse Drug Events

Fibric acid derivatives are fairly well tolerated. No clear differences seem to exist with regard to side effects between the drugs in this class. Myopathy and rhabdomyolysis have been rarely reported with fibric acid derivative therapy. The most common adverse drug events reported with the fibric acid derivatives are noted in Table 7.

Table 7. Adverse Drug Events (%) Reported with Fibric Acid Derivatives[10-15]

Adverse Event(s)	Fenofibrate	Gemfibrozil
Cardiovascular		
Angina pectoris	✔	-

Adverse Event(s)	Fenofibrate	Gemfibrozil
Arrhythmia	✔	-
Atrial fibrillation	✔	1
Cardiovascular disorder	✔	-
Coronary artery disorder	✔	-
Edema	✔	-
Electrocardiogram abnormal	✔	-
Hypertension	✔	-
Hypesthesia	-	✔
Hypotension	✔	-
Migraine	✔	-
Myocardial infarction	✔	-
Palpitation	✔	-
Peripheral edema	✔	-
Peripheral vascular disorder	✔	✔
Phlebitis	✔	-
Syncope	-	✔
Tachycardia	✔	-
Varicose vein	✔	-
Vascular disorder	✔	-
Vasodilatation	✔	-
Ventricular extrasystoles	✔	-
Central Nervous System		
Anxiety	✔	-
Confusion	-	✔
Convulsion	-	✔
Depression	✔	✔
Dizziness	✔	✔
Fatigue	-	4
Fever	✔	-
Headache	3	1
Hypertonia	✔	-
Insomnia	✔	-
Libido decreased	✔	✔
Nervousness	✔	-
Neuralgia	✔	-
Paresthesia	✔	✔
Pain	✔	-
Peripheral neuritis	-	✔
Somnolence	✔	✔
Vertigo	✔	2
Dermatological		
Acne	✔	-
Alopecia	✔	-
Angioedema	-	✔
Contact dermatitis	✔	-
Eczema	✔	2
Exfoliative dermatitis	-	✔
Fungal dermatitis	✔	-
Herpes simplex	✔	-
Herpes zoster	✔	-
Nail disorder	✔	-

Adverse Event(s)	Fenofibrate	Gemfibrozil
Maculopapular rash	✔	-
Photosensitivity reaction	✔	✔
Pruritus	✔	-
Rash	-	2
Skin disorder	✔	-
Skin ulcer	✔	-
Stevens-Johnson syndrome	✔	-
Sweating	✔	-
Toxic epidermal necrolysis	✔	-
Urticaria	✔	✔
Vasculitis	-	✔
Endocrine and Metabolic		
Diabetes mellitus	✔	-
Gout	✔	-
Gynecomastia	✔	-
Hypoglycemia	✔	-
Hyperuricemia	✔	-
Gastrointestinal		
Abdominal pain	5	10
Anorexia	✔	-
Cholestatic jaundice	-	✔
Colitis	✔	-
Constipation	2	1
Diarrhea	2	7
Duodenal ulcer	✔	-
Dyspepsia	✔	20
Eructation	✔	-
Esophagitis	✔	-
Flatulence	✔	-
Gastritis	-	-
Gastroenteritis	-	-
Gastrointestinal disorder	-	-
Increased appetite	-	-
Nausea	2	-
Nausea and vomiting	-	2
Peptic ulcer	✔	-
Rectal disorder	-	-
Rectal hemorrhage	-	-
Vomiting	✔	-
Weight gain/loss	✔	-
Genitourinary		
Creatinine increased	✔	-
Cystitis	✔	-
Decreased male fertility	-	✔
Dysuria	✔	-
Impotence	-	✔
Kidney function abnormal	✔	✔
Nephrotoxicity	-	✔
Prostatic disorder	✔	-
Unintended pregnancy	✔	-
Urinary frequency	✔	-

Adverse Event(s)	Fenofibrate	Gemfibrozil
Vaginal moniliasis	✔	-
Hematologic		
Agranulocytosis	✔	-
Anemia	✔	✔
Ecchymosis	✔	-
Eosinophilia	✔	-
Leukopenia	✔	✔
Lymphadenopathy	✔	-
Thrombocytopenia	✔	✔
Hepatic		
Alkaline phosphokinase increased	-	✔
Alanine aminotransferase increased	3	✔
Aspartate aminotransferase increased	3	✔
Bilirubin increased	-	✔
Cholecystitis	✔	✔
Cholelithiasis	✔	✔
Creatinine phosphokinase increased	3	✔
Jaundice	-	✔
Liver fatty deposit	✔	-
Musculoskeletal		
Arthralgia	✔	✔
Arthritis	✔	-
Arthrosis	✔	-
Bursitis	✔	-
Back pain	3	-
Joint disorder	✔	-
Leg cramps	✔	-
Muscle pain	✔	-
Myalgia	✔	-
Myasthenia	✔	✔
Myopathy	✔	✔
Myositis	✔	-
Painful extremities	-	✔
Paresthesia	✔	✔
Rhabdomyolysis	✔	✔
Synovitis	-	✔
Tenosynovitis	✔	-
Weakness	✔	-
Respiratory		
Asthma	✔	-
Bronchitis	✔	-
Cough increased	✔	-
Dyspnea	✔	-
Laryngeal edema	-	✔
Laryngitis	✔	-
Pharyngitis	✔	-
Pneumonia	✔	-
Respiratory disorder	6	-
Rhinitis	2	-
Sinusitis	✔	-
Other		

Adverse Event(s)	Fenofibrate	Gemfibrozil
Allergic reaction	✔	-
Amblyopia	✔	-
Anaphylaxis	-	✔
Appendicitis, acute	-	1
Asthenia	2	-
Blurred vision	-	✔
Cataracts	✔	✔
Chest pain	✔	-
Conjunctivitis	✔	-
Cyst	✔	-
Drug-induced lupus syndrome	-	✔
Dry mouth	✔	-
Ear pain	✔	-
Eye disorder	✔	-
Flu syndrome	2	-
Hernia	✔	-
Infection	✔	-
Intracerebral hemorrhage	-	✔
Hypersensitivity reaction	✔	-
Malaise	✔	-
Otitis media	✔	-
Pancreatitis	-	✔
Raynaud’s phenomenon	-	✔
Refraction disorder	✔	-
Retinal edema	-	✔
Seizure	-	✔
Syncope	-	✔
Taste perversion	-	✔
Vision abnormalities	✔	-

✔ Percent not specified
- Event not reported or incidence <1%

VII. Dosing and Administration

The usual dosing regimens for the fibric acid derivatives are summarized in Table 8.

Table 8. Usual Dosing for the Fibric Acid Derivatives[1,10-15,17,18]

Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
Fenofibrate, micronized (Antara®)	Primary Hypercholesterolemia or Mixed Hyperlipidemia: Initial: 130 mg daily Hypertriglyceridemia: Initial: 43-130 mg daily; maximum: 130 mg/day	Safety and efficacy have not been established in children.	Capsules: 43 mg 130 mg
Fenofibrate, micronized (Lipofen®)	Primary Hypercholesterolemia or Mixed Hyperlipidemia: Initial: 150 mg daily Hypertriglyceridemia: Initial: 50-150 mg daily; maximum: 150 mg/day	Safety and efficacy have not been established in children.	Capsules: 50 mg 150 mg
Fenofibrate, micronized	Primary Hypercholesterolemia or Mixed Hyperlipidemia:	Safety and efficacy have not been established in children.	Capsules: 67 mg

Drug	Usual Adult Dose	Usual Pediatric Dose	Availability
(Lofibra® and equivalents)	Tablet: initial, 160 mg daily Capsule: initial, 200 mg daily Hypertriglyceridemia: Tablet: initial, 54-160 mg daily; maximum: 160 mg/ day Capsule: initial, 67-200 mg daily; maximum: 200 mg/day		134 mg 200 mg Tablet: 54 mg 160 mg
Fenofibrate, micronized (Triglide®)	Primary Hypercholesterolemia or Mixed Hyperlipidemia: Initial: 160 mg daily Hypertriglyceridemia: Initial: 50-160 mg daily; maximum: 160 mg/day	Safety and efficacy have not been established in children.	Tablets: 50 mg 160 mg
Fenofibrate, nanocrystallized (Tricor®)	Primary Hypercholesterolemia or Mixed Hyperlipidemia: Initial: 145 mg daily Hypertriglyceridemia: Initial: 48-145 mg daily; maximum: 145 mg/day	Safety and efficacy have not been established in children.	Tablets: 48 mg 145 mg
Gemfibrozil	Type IIb Dyslipidemia or Hypertriglyceridemia: Initial and maintenance: 600 mg twice daily; maximum: 1,200 mg/day	Safety and efficacy have not been established in children.	Tablets: 600 mg

VIII. Effectiveness

Table 9 below summarizes clinical studies evaluating the safety and efficacy of the fibric acid derivatives.

Table 9. Comparative Clinical Trials Using the Fibric Acid Derivatives

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Coronary Arteriosclerosis: Prophylaxis				
Keech et al[19] FIELD Fenofibrate 200 mg DAILY vs placebo	DB, PC, R Patients aged 50-75 years with type 2 diabetes mellitus	N=9,975 5 years	Primary: Coronary events (CHD, death or nonfatal MI) Secondary: Total cardiovascular events which included the composite of cardiovascular death, MI, stroke, and coronary and carotid revascularization; total mortality	Primary: 5.9% (N=288) of patients on placebo and 5.2% (N=256) of those on fenofibrate had a coronary event (relative reduction of 11%; HR, 0.89; 95% CI, 0.75 to 1.05; *P*=0.16). This finding corresponds to a significant 24% reduction in nonfatal myocardial infarction (HR, 0.76; 95% CI, 0.62 to 0.94; *P*=0.010) and a nonsignificant increase in coronary heart disease mortality (HR, 1.19; 95% CI, 0.90 to 1.57; *P*=0.22). Secondary: Total cardiovascular disease events were significantly reduced from 13.9% to 12.5% (HR, 0.89; 95% CI, 0.80 to 0.99; *P*=0.035). This finding included a 21% reduction in coronary revascularization (HR, 0.79; 95% CI, 0.68 to 0.93; *P*=0.003). Total mortality was 6.6% in the placebo group and 7.3% in the fenofibrate group (*P*=0.18).
DAIS[20] Micronized fenofibrate 200 mg DAILY vs placebo	PC, R Men and women with type 2 diabetes with good glycemic control, who had mild lipoprotein abnormalities typical of type 2 diabetes and at least one visible coronary lesion	N=418 3 years	Primary: Mean percentage stenosis, minimum coronary artery lumen diameter, mean segment diameter Secondary: Not reported	Primary: Plasma TC, HDL-C, LDL-C, and TG concentrations all changed significantly more from baseline in the fenofibrate group (N=207) than in the placebo group (N=211). The fenofibrate group showed a significantly smaller increase in percentage diameter stenosis than the placebo group (mean 2.11 vs 3.65; *P*=0.02), a significantly smaller decrease in minimum lumen diameter (–0.06 vs –0.10 mm; *P*=0.029), and a nonsignificantly smaller decrease in mean segment diameter (–0.06 vs –0.08 mm; *P*=0.171). The trial was not powered to examine clinical end points. Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Not reported
Frick, Elo et al[21] Helsinki Heart Study Gemfibrozil 600 mg BID vs placebo	DB, R Asymptomatic middle-aged men (40 to 55 years of age) with primary dyslipidemia (non–HDL-C $\geq$ 200 mg/dL in 2 consecutive pretreatment measurements)	N=4,081 5 years	Primary: Risk of CHD measured by incidence of cardiac events Secondary: Total mortality	Primary: There were minimal changes in serum lipid levels in the placebo group. The cumulative rate of cardiac end points at five years was 27.3 per 1,000 in the gemfibrozil group and 41.4 per 1,000 in the placebo group, a reduction of 34% in the incidence of CAD (95% CI, 8.2 to 52.6; *P*<0.02; two-tailed test). The decline in incidence in the gemfibrozil group became evident in the second year and continued throughout the study. Secondary: There was no difference between the groups in the total death rate, nor did the treatment influence the cancer rates.
Frick, Heinonen et al[22] Helsinki Heart Study Gemfibrozil 600 mg BID vs placebo	DB, R Individuals who exhibited symptoms and signs of possible CHD during screening in the Helsinki Heart Study	N=311 5 years	Primary: Risk of CAD measured by incidence of cardiac events Secondary: Total mortality	Primary: The end point rate, consisting of fatal and nonfatal MI and cardiac death, did not differ significantly between the placebo and gemfibrozil groups. Since there were key prognostic factors missing (eg, true prevalence of CHD, extent of coronary artery obstructions, degree of left ventricular dysfunction, and their distribution in the groups render the results less reliable), the data cannot be used to refute the thesis that treatment of dyslipidemia in manifest CHD is successful. Secondary: Total mortality did not differ significantly between the placebo and gemfibrozil groups.
Heinonen et al[23] Helsinki Heart Study Gemfibrozil 600 mg BID vs placebo	DB, MC Asymptomatic middle-aged men (40 to 55 years of age) with non–HDL-C greater than or equal to 200 mg/dL in 2 consecutive pretreatment	N=2,046 3.5 years	Primary: Definite fatal and nonfatal CHD events Secondary: Not reported	Primary: During the posttrial period the numbers of definite CHD events in both groups (54 vs 47; *P*=NS) were smaller than expected without treatment, namely a reduction of around 40% for the original treatment groups. The mean incidence rates were in fact similar to that in the placebo group 5 years earlier. Cardiovascular mortality over the entire study period was similar but all-cause mortality was slightly higher among men of the original gemfibrozil group compared to the placebo group men (*P*=0.19). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	measurements)			Not reported
Robins et al[24] VA-HIT Gemfibrozil 1,200 mg daily vs placebo	DB, MC, PC, R Men with a history of CHD who had low HDL-C levels and low LDL-C levels	N=2,531 7 years	Primary: Nonfatal MI or death from coronary causes Secondary: Not reported	Primary: Compared to placebo, gemfibrozil showed a 22% decreased risk of nonfatal MI or death due to CHD (17.3% gemfibrozil vs 21.7% placebo; *P*=0.006). Compared to placebo, gemfibrozil showed a 24% decreased risk for nonfatal MI, death due to CHD or confirmed stroke (20% gemfibrozil vs 26% placebo; *P*<0.001). A nonsignificant difference was seen in all-cause mortality with gemfibrozil compared to placebo (15.7% gemfibrozil vs 17.4% placebo; *P*=0.23). Concentrations of HDL-C were inversely related to CHD events. Multivariable Cox proportional hazards analysis showed that CHD events were reduced by 11% with gemfibrozil for every 5 mg/dL (0.13 mmol/L) increase in HDL-C (*P*=0.02). Events were reduced even further with gemfibrozil beyond that explained by increases in HDL-C values, particularly in the second through fourth quintiles of HDL-C values during treatment. During gemfibrozil treatment, only the increase in HDL-C significantly predicted a lower risk of CHD events; according to multivariable analyses, neither TG nor LDL-C levels at baseline or during the trial predicted CHD events. Secondary: Not reported
Hypertriglyceridemia				
Rosenson et al[25] Fenofibrate 160 mg DAILY vs placebo	DB, PC, R Patients with fasting hypertriglycer-idemia (≥1.7 and <6.9 mmol/L) and 2 or more of the NCEP ATP	N=59 19 weeks	Primary: Fasting TG, postprandial TG, oxidative stress, inflammatory response Secondary: Not reported	Primary: Fenofibrate treatment lowered fasting TG (–46.1%; *P*<0.0001) and postprandial (area under the curve) TG (–45.4%; *P*<0.0001) due to significant reductions in postprandial levels of large (–40.8%; *P*<0.0001), medium (–49.5%; *P*<0.0001) and VLDL particles. The number of fasting total LDL particles was reduced in fenofibrate-treated subjects (–19.0%; *P*=0.0033) primarily due to reductions in small LDL particles (–40.3%; *P*<0.0001); these treatment differences persisted postprandially.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	III criteria for the metabolic syndrome			Fasting and postprandial oxidized fatty acids were reduced in fenofibrate-treated subjects compared with placebo-administered subjects (–15.3%; *P*=0.0013, and 31.0%; *P*<0.0001, respectively). Fenofibrate therapy lowered inflammatory markers as follows: fasting and postprandial soluble VCAM-1 decreased by –10.9% for fasting VCAM-1 (*P*=0.0005), and by –12.0% for postprandial VCAM-1 (*P*=0.0001); and fasting and postprandial soluble ICAM-1 decreased by –14.8% for fasting ICAM-1 (*P*<0.0001) and by –15.3% for postprandial ICAM-1 (*P*<0.0001). Reductions in VCAM-1 and ICAM-1 were correlated with reductions in fasting and postprandial large VLDL particles (*P*<0.0001) as well as postprandial oxidized fatty acids (*P*<0.0005). Secondary: Not reported
Davidson et al[26] TRIMS Micronized fenofibrate 130 mg DAILY vs placebo	DB, MC, PC, RCT Patients between the ages of 21 and 79 years, with fasting TG levels ≥300 and <1,000 mg/dL, and at least two of four additional components of the metabolic syndrome as defined by the NCEP ATP III	N=146 8 weeks	Primary: Changes or percent changes from baseline to the end-of-treatment in fasting TG Secondary: Changes or percent changes from baseline in TC, LDL-C, HDL-C, the TC:HDL-C ratio, VLDL-C, non–HDL-C; apo AI, B, and C-III; and remnant lipoprotein cholesterol	Primary: There was a significant change from baseline in the mean percent decrease of TG in the fenofibrate group (36.6%) compared with essentially no change in the placebo group (*P*<0.001). Secondary: There was no significant difference in TC change between the fenofibrate treatment and the placebo groups (*P*=0.085). LDL-C increased by a mean of 15.0% in the fenofibrate group compared with 3.2% in the placebo group (*P*=0.006). HDL-C increased by a mean of 14.0% in the fenofibrate group compared with 0.8% for placebo (*P*<0.001). The ratio of TC to HDL-C decreased with fenofibrate compared with placebo (–14.2% vs 0.8%; *P*<0.001). VLDL-C declined by 33% with fenofibrate compared with a 1.6% decline with placebo treatment (*P*<0.001). Non–HDL-C decreased significantly more in the fenofibrate group (–7.5% vs –1.1%; *P*=0.009).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				There was no significant difference in the rise in apo AI among the fenofibrate group vs the placebo response (5.3% vs 2.0%; *P*=0.212). Apo B declined significantly with fenofibrate compared with placebo (*P*<0.001, respectively). Apo CIII was markedly reduced in the fenofibrate group (*P*<0.001 compared with placebo). A significant reduction in remnant lipoprotein cholesterol was observed with fenofibrate treatment (–35.1% vs an increase of 12.3%; *P*<0.001).
Koh et al[27] Fenofibrate 200 mg DAILY plus placebo vs fenofibrate 200 mg DAILY plus candesartan 16 mg DAILY vs candesartan 16 mg DAILY plus placebo	DB, PC, R, XO Patients with hypertriglyceri-demia (≥150 mg/dL) and hypertension (≥140/90 mm Hg)	N=46 6 months	Primary: Blood pressure, lipid profile, inflammatory markers, vasomotor function, plasma malondialdehyde, adioponectin, and insulin resistance Secondary: Not reported	Primary: Fenofibrate, combined therapy, or candesartan therapy significantly reduced blood pressure. However, combined therapy significantly reduced blood pressure more than fenofibrate or candesartan alone (*P*<0.001). When compared with candesartan, fenofibrate or combined therapy significantly improved the lipoprotein profile. Fenofibrate alone or combined therapy significantly lowered TC, TG, apo B, and non–HDL-C levels (all *P*<0.001) and increased HDL-C levels (*P*<0.001) when compared with baseline. These reductions were significantly greater than those observed with candesartan alone (*P*<0.001). However, there were no significant differences between fenofibrate alone and fenofibrate plus candesartan for these parameters (*P*=NS). All three treatment arms significantly improved flow-mediated dilator response to hyperemia. Combined therapy significantly decreased plasma malondialdehyde (a biomarker for oxidative stress), hsCRP, and soluble CD40L levels relative to baseline measurements. Importantly, these parameters were changed to a greater extent with combined therapy when compared with monotherapy (*P*<0.001, *P*=0.002, *P*=0.050, and *P*=0.032, respectively). Fenofibrate, combined therapy, and candesartan significantly increased plasma adiponectin levels and insulin sensitivity relative to baseline measurements. However, the magnitudes of these increases were not significantly different among the three therapies (*P*=0.246 for adiponectin levels and *P*=0.153 for insulin sensitivity). Secondary: Not reported
Treatment of Primary Hypercholesterolemia or Mixed Dyslipidemia				

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Farnier, Freeman et al[28] Fenofibrate 160 mg DAILY vs fenofibrate 160 mg DAILY plus ezetimibe 10 mg DAILY vs ezetimibe 10 mg DAILY vs placebo	DB, MC, PA, PC, R Patients with mixed hyperlipidemia and no CHD or CHD-risk equivalent disease, or 10-year CHD risk >20% according to NCEP ATP III criteria	N=625 12 weeks	Primary: Percent change in LDL-C from baseline to study end point after treatment with fenofibrate plus ezetimibe vs fenofibrate alone Secondary: Percent change from baseline to study end point in TC, TG, non–HDL-C, HDL-C, apo B, apo AI	Primary: There was a significantly greater percent reduction in LDL-C among patients in the fenofibrate plus ezetimibe group vs the fenofibrate only group (*P*>0.001). Secondary: Non–HDL-C and apo B were significantly reduced with fenofibrate plus ezetimibe when compared with fenofibrate or ezetimibe alone (*P*>0.001). TG levels were significantly decreased and HDL-C was significantly increased with fenofibrate plus ezetimibe when compared with placebo (*P*<0.001).
Farnier, Roth et al[29] Fenofibrate 160 mg DAILY vs simvastatin-ezetimibe 20 mg-10 mg combination tablet DAILY plus fenofibrate 160 mg DAILY	DB, MC, PA, PC, R Patients 18 to 79 years old with mixed hyperlipidemia and no CHD or CHD-risk equivalent disease, or 10-year CHD risk >20% according to NCEP ATP III	N=611 12 weeks	Primary: Percent change in LDL-C from baseline to study end point Secondary: Percent change from baseline to study end point in TC, TG, non–HDL-C, HDL-C, apo AI, and apo B	Primary: LDL-C level was significantly reduced with simvastatin-ezetimibe plus fenofibrate (–45.8%) compared with fenofibrate (–15.7%) or placebo (–3.5%; *P*<0.01), but not when compared with simvastatin-ezetimibe (–47.1%; *P*>0.2). Secondary: HDL-C and apo AI levels were significantly increased with simvastatin-ezetimibe plus fenofibrate (18.7% and 11.1%; *P*<0.01, respectively) treatment compared with simvastatin-ezetimibe (9.3% and 6.6%; *P*<0.01) or placebo (1.1% and 1.6%; *P*<0.01), but not when compared with fenofibrate (18.2% and 10.8%; *P*>0.2). TG, non–HDL-C, and apo B levels were significantly reduced with simvastatin-ezetimibe plus fenofibrate (–50.0%, –50.5%, and –44.7%; *P*<0.01, respectively) vs all other treatments.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs simvastatin-ezetimibe 20 mg-10 mg combination tablet DAILY vs placebo	criteria			
McKenney et al[30] Fenofibrate 160 mg DAILY vs fenofibrate 160 mg DAILY plus ezetimibe 10 mg DAILY vs ezetimibe 10 mg DAILY for first 12 weeks, then switched to fenofibrate plus ezetimibe DAILY for 48 week extension phase vs placebo for first 12	DB Patient who completed base study with mixed hyperlipidemia	N=576 48 weeks	Primary: Percent change in LDL-C from baseline of the base study to study end point in the extension Secondary: Percent change from baseline to study end point in TC, HDL-C, TG, non–HDL-C , apo B, apo AI, and hsCRP	Primary: Fenofibrate plus ezetimibe showed significantly greater percent reductions in LDL-C compared with fenofibrate alone (–22.0 vs –8.6; P<0.001). Fenofibrate plus ezetimibe showed significantly greater percent reductions from baseline to extension study end point in TC (–23.2 vs –13.6; P<0.001), TG (–46.0 vs –41.0; P=0.002), non–HDL-C (–31.6 vs –19.4; P<0.001), and apo B (–25.2 vs –16.2; P<0.001) compared with fenofibrate. There was a significantly greater percent increase in HDL-C (20.9 vs 17.8; P=0.02) with fenofibrate plus ezetimibe vs fenofibrate alone. There was not a significantly greater percent increase in apo AI (10.1 vs 7.8; P=0.12) with fenofibrate plus ezetimibe vs fenofibrate alone. Reductions in median hsCRP levels were not different between treatments (–25.3 vs –21.1; P=0.46) for fenofibrate plus ezetimibe vs fenofibrate alone, respectively.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
weeks, then switched to fenofibrate for 48 week extension phase				
Insua et al[31] Gemfibrozil 900 mg daily vs micronized fenofibrate 200 mg DAILY	DB, DD, R, XO Patients between the ages of 45 and 70 years with primary hyperlipo-proteinemia, Fredrickson phenotypes IIa and IIb	N=21 6 weeks	Primary: Cholesterol-lowering effectiveness Secondary: Not reported	Primary: Both drugs significantly reduced TC, calculated LDL-C, TG, apo B, and fibrinogen (*P*<0.01 for all calculations, except *P*<0.05 for fibrinogen with gemfibrozil therapy) and increased HDL-C (*P*<0.01). Neither drug affected Lp (a) lipoprotein, whereas uric acid was reduced only by fenofibrate (*P*<0.01). The percentage decrease in TC and LDL cholesterol was greater with fenofibrate than with gemfibrozil (–22% versus –15%; *P*<0.02; and –27% versus –16%; *P*<0.02, respectively). In contrast, reductions in levels of TG (–54% vs –46.5%), apo B, and fibrinogen, as well as the increase in HDL (+9% for both drugs), showed no significant difference between treatments. Separate analysis of patients with type IIb hyperlipoproteinemia showed essentially the same plasma lipid changes as for the overall group, but with greater modifications in TG and HDL concentrations. Secondary: Not reported
Conversion Between Fibric Acid Derivatives				
Corbelli et al[32] Gemfibrozil, mean daily dose 1,200 mg/day to fenofibrate, mean daily dose of 201	RETRO Patients who were switched from gemfibrozil to fenofibrate, due to inadequate lipid response or adverse effects	N=92 23 months	Primary: Mean TC, TG, HDL, and non-HDL Secondary: Not reported	Primary: Compared to gemfibrozil, patients showed statistically significant improvements in mean TC, TG, HDL, and non-HDL (*P*<0.005). Specifically, more patients achieved a TG goal < 200 mg/dL with fenofibrate (64%) compared to gemfibrozil (39%; *P*<0.0005). The study demonstrated that patients switched from gemfibrozil to fenofibrate due to an inadequate lipid response experienced significant improvements in lipid parameters for up to 18 months.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
mg/day				Secondary: Not reported

Drug regimen abbreviations: BID=twice daily
Study abbreviations: CI=confidence interval, DB=double-blind, DD=double dummy, HR=hazard ratio, MC=multicenter, PA=parallel arm, PC=placebo controlled, R=randomized, RCT=randomized controlled trial, RETRO=retrospective study, XO=crossover
Miscellaneous abbreviations: apo=apoliprotein, CHD=coronary heart disease, DAIS=Diabetes Atherosclerosis Intervention Study, FIELD=Fenofibrate Intervention and Event Lowering in Diabetes, HDL=high-density lipoprotein, HDL-C= high-density lipoprotein cholesterol, ICAM-1=intercellular adhesion molecule-1, LDL=low-density lipoprotein, LDL-C=LDL cholesterol, MI=myocardial infarction, NCEP ATP III=National Cholesterol Education Program Adult Treatment Panel III, non–HDL-C=non–high-density lipoprotein cholesterol, TC=total cholesterol, TG=triglycerides, TRIMS=Triglyceride Reduction in Metabolic Syndrome, VA-HIT=Veterans Affairs High-Density Lipoprotein Intervention Trial, VCAM-1=vascular cell adhesion molecule-1, VLDL=very low-density lipoprotein, VLDL-C=very low-density lipoprotein cholesterol

IX. Conclusions

It has been shown that lowering cholesterol (including low-density lipoprotein cholesterol [LDL-C]) significantly reduces cardiovascular risk. Because LDL-C is the major atherogenic lipid component, the NCEP ATP III guidelines focus primarily on attaining designated LDL-C goals. While LDL-C is the primary treatment target, very high triglycerides (TG) should also be treated to avoid pancreatitis and reduce coronary heart disease (CHD) risk. Finally, consideration should be given to treating low levels of high-density lipoprotein cholesterol (HDL-C) despite LDL-C goal attainment.

Fibric acid derivatives are used less frequently than HMG-CoA reductase inhibitors (or statins), primarily because of a reduced LDL-C lowering capacity compared to statins; however, they have a greater capacity to reduce TG compared to statins. The main place in therapy for fibric acid derivatives is for the treatment of hypertriglyceridemia in patients at risk for pancreatitis and hypertriglyceridemia in patients with low HDL-C, especially with underlying diabetes, insulin resistance or the metabolic syndrome.[33]

Gemfibrozil and fenofibrate are available generically. There are numerous formulations of fenofibrate, among which no particular product offers a distinct clinical advantage over another. There are no major clinically relevant differences between gemfibrozil and fenofibrate with regard to TG-lowering efficacy, tolerability, or safety. Notably, both gemfibrozil and fenofibrate are supported by clinical trials that show reductions in patient-oriented outcomes (CHD morbidity and/or mortality).[19,21-24] However, neither product has demonstrated a decrease in all-cause mortality as has been shown with the statins. The national and international consensus treatment guidelines do not give preference to one fibric acid derivative over another. Both gemfibrozil and fenofibrate should be administered cautiously with a concomitant statin; however, there is evidence to suggest that fenofibrate may have less of an effect on statin metabolism and/or levels.

X. Recommendations

In recognition of the well-established role of the fibric acid derivatives for the treatment of hypertriglyceridemia, and the lack of well-documented clinically significant differences in efficacy amongst the products, no changes are recommended to the current approval criteria.

Gemfibrozil and Tricor® are preferred on The Office of Vermont Health Access (OVHA) preferred drug list.

Lopid® requires prior authorization with the following approval criteria:

- The patient has had a documented intolerance to generic gemfibrozil.

Tricor® requires prior authorization when a statin is not found in the patient drug file at POS. with the following approval criteria.

- The patient has been started and stabilized on the requested medication.

<u>OR</u>

- The patient is taking a statin concurrently.

<u>OR</u>

- The patient has had a documented side effect, allergy, or treatment failure to gemfibrozil.

Antara®, fenofibrate, fenofribrate micronized, Fenoglide®, Lipofen®, Lofibra® and Triglide® require prior authorization with the following approval criteria:

- The patient is taking a statin concurrently and has had a documented side effect, allergy, or treatment failure with Tricor.

<u>OR</u>

- The patient has had a documented side effect, allergy, or treatment failure to gemfibrozil and Tricor®.

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